Cimetidine: does neurotoxicity occur? Report of three cases

M E Edmonds asc made R F U Ashford MA MACE M K Bromer MA MACE A Saunders MD MACE

Departments of Therspectus's and Rhenmardings, Westmasser Hospital, London SWIP 24P, and St Stephen's Hospital, Landon SWIOSTH

There have been several reports of neurotoxicity attributed to cinetidine. These include confusion (Grinson 1977, Delaney & Raven 1977, McMillen et al. 1978, Wood et al. 1978) and twitching (Grave et al. 1977). In none have plasma cinetidine estimations been performed Here we report three cases of neurotoxicity in which the plasma eimetidine concentration was estimated. Cinetidine was present in the CSF of two of the cases. The causality role of cimetidine is discussed.

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A 3x year old womin with a past history of discretables presented with lower old ominal pain. After a period of conservative management with antibiotics laparotomy was performed. A perforance periodic absence, peneralized portonitis, and subphrenic absences were found. The pleasures were drained and a transverse colorious performed. Postoperative complication were pulmonary ordena, wound infection with factal fixuda formation and recorrent subplication absects. Intertion was treated with beneatpenfollim, metropidatole and performed. Following explanation of the left subplantate space she again developed pulmentary of demaand required temporary ventilation. Six developed oligaria which, despite discontinuing pentantical, progressed to anoma Cinetidate syrup 100 mg six hearly was started following aspiration of blood via the assopastric tribe. She was havined allowed for these weeks during which time the received cimendine 200 mg eight hours; i.e. She was drower throughout. When appearance is directly commenced, had adulty is was stopped. Three days later she because confused and following a right Jacksonian fit, developed status epilepticus. This was uncontrolled by disception 20 mg (.v., phenytoin 90) mg (.m., 10 mi 10°, valeium glaccasate sed Zmi Sit magnesium sulphane Thiopenions 350 mg i.v. hourly was necessary to achieve controj. At this time plasma sodium was 139, potassium 3,3, prea 200, glacose 6,3 mwell-CSF showed RBC 0, WBC 0, protein 9-12 gd, CAT was was normal. Plasma dimension concentration was 7.5 mg/Laud CSF capetidisc concentration 0.82 mg/l (hegb pressury injus chromation agree method) (Randolph et al. 1977). She was also receiving benzylpeniallin 🖂 megaunits eight hourly Lv., gentamion 60 mg Lv. daily (with plasma level monitor or) and metronidazole 2 g cight hourly per recount for persistent sepsis. Metronidazola levels were low at 28.8 mg of (polyrographic method) (Kane 1961). Cinadding was reduced to 200 mg (x daily Pennilla, gertamich and metropidatele were dopped. She becovered conscious and had no further fits. Subsequently renal function recovered but receptoration of the abdomen I months later revealed an adenocarcinema of the left overy and the patient Normal Come Garage subsequently died.

Case 2: - ×

A 12-year-old man with osteoarthritis, gout, psoriosis, hypertension and mild chrome rensitioner, successful a gaptrointestinal bleed whilst an inputient. He was on ampropagate 200 mg

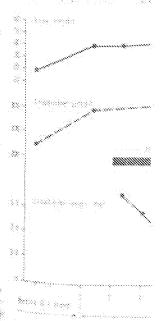
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ax kettrly. Prior to this c ercatisane 250 pm dil H The past day by becom emetidine concentration 39.3 mmol land creating ea the third day of chuck He continued to bleed. eatheterization. After this of the twitching had forth 4.57 mg/L Uros was Sld that day be underwern go Postoperatively cimetidir priching was again craft dosci was 2.92 mg/l and enduced to 100 mg six concentration (2 h 30 m 320 amol/L No twitching had a further melacha an day the patient became Cinclinic concentration continue 225 pmoli) (c Cartesian day the penen difficulties concentration stra had follon to 11,3 m confused or twitching. Th the clinical course of this:

Case 3 A 51-year-old man was ad With Newsylpenicillin, Hys



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americine. These include 1978. Weed coal. (978) and romations been performed. metaling concentration was ares. The causative role of

with lower abdominal pair. rotono was performed A a absocises were feated. The assessors time committeeties.

formation and recurrent conidazoic and contamicio. eleped pulmonary ocdema uch, despite discontinuing outly was started following sed for three weeks during adrowsy throughout. When firee days later she become aus epikoricus. This was 10° calcrom glacemate and was necessary to achieve a 2000, glassione 6,3 mmol/L permit. Plasma cimetidist I me i thigh pressure liquid ceiving bearstpendillin 13 sma level mosilorings and tronidazole levels were low vas reduced to 200 mg is. se recovered consciousness but reexploration of the off every and the patient

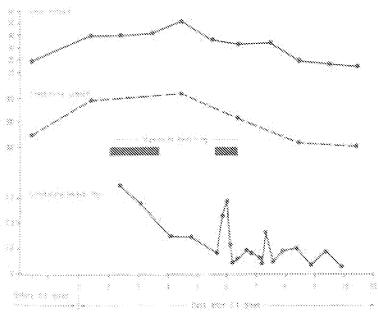
on and mild chronic repair e- on axapropazone 300 ms

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as honely. Prior to this event like creatinine clearance was 13 mil minute, area 18,3 minol/l, and Accoming 250 pmoi L Ne was transfused and stanted on himending 200 mg gight hoursely i.e. the next day he became confused and widespread muscular twitching was noted. Plasma geordine concentration was 2.52 mg (4 hours after his first dose of cimendine). His offic way 70.7 Juniol 1 and creatinate 230 amol 1. Constitute was reduced to 200 any twice gally i.v. and on the third day of constiding therapy twitching was less noticeable and he was less confused. ng communitie bleed, was further transmissed and required original dilatation prior to _{cathere}ctization. After this he had a pood diversis. On the fourth day the frequency and extent of the twitching had further lessened. Plasma cimeriding concentration (90 min after dose) was 157 mg/l. Urea was 31.0 mmol/l and creatining 430 jumol/l. Pollowing a further bleed later and day he underwent gastroduccionotomy, vagotomy and oversewing of three pyloric nicers. Per operatively simulating was instrusted to 200 mg as hourly and on the next (fifth) day the plasme THE BEET WAS COMED FOR DUTIES AND RESERVED TO PROPERTY FOR THE SERVED CONCENTRATION FOR THE SERVED AND THE SERV keistell to 100 die au hourly und the twinting was too evident. Plasma emetiding gracerstation (24 30 men after dose) was 0.95 mg/, lives 32.5 mmel/ and creationed 420 pined J. No twistling was objected on the separate day but at 18,00 that day the patient tal a facility mediana and consolidate was markaged to 29 mg sight hearly by. On the engith In the patient became more confused but he further assembly was observed. Plasma Sopricine concentration (2 is 30 min after dose) was L14 mg/, pres 20.0 mmol/, and southern 21.5 pmol/. He was transfused again but after this but no further beeds. On the connecrets day the patient was changed to concuding 200 mg eight hearly erally. The plasma generative concentration (30 min after descious 2.16 mg/) on the sixteenth day. By then the figs had fallen to 11.3 mmob) and creatinine was 120 pmob), and the patient was no longer confused on twitching. The biased sires, creatinine and plasma cinicitiding concentration during

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 λ 62 -year-old man was admitted to hospital with prenmococcal greatments which was treated with berievipensedlin. Hypsicikaemia and tetany of unknown activiogy developed 24 hours



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Two days later, following a harmatements he was started on concluding 200 mg twice daily 1.5 which was subsequently increased to 200 mg air houristly. Twenty-four hours later (after a deser) be developed grand mal convulsions succentroliable by conventional anticonvolvings. Control was obtained by curarization and intravenous infusion of thiopentons. Repeat lumber paneture was suchanged. Plasma sodium, potassium, calcium and magnesium were all normal. Urea was 35.0 minut. The plasma concentration was 1.75 mg 1. USF cimetidine concentration was 0.76 mg 1. Cimetidine was discontinued and after 24 hours no further convulsions occurred, although he did not fally regain consciousness. He subsequently developed pseudomonas separatemia and died. Permission for autopsy was refused.

Disconsting

Although the neurotoxicity described in these cases is multifactorial we believe concliding played an important role in Cases 1 and 3. In Case 1 in spite of renal impairment and sepsis we found no metabolic of infective cause for the convulsions. The dose of penicilin was not expensive. Metronidazole levels were low and we know of no reports of this agent causing convulsions. Plasma circuiding concentration was high at 7.5 mg L (Normal range 2 bours after dose: 0.5-3.0 mg/h, CSF cimendide was 0.22 mg/l. Cimendide accumulation accumula when hadmodisly-se was discontinued, as the usual route of climination via the urine was not evallable. The grow is cleared well by hacocodialysis (Canavan et al. 1977). In Case 2, the aggerrance of twitching correlated will the plasma cimeridine concentration only whilst the patient was urnemic. There was no correlation between the plasma cimetaline concentration and mental confusion in this parient (see Figure 1). In Case 3 consulsions occurred only whilst the patient was on cimetidate; however, there is a 25 per cent incidence of convulsions in presimple contain manifest (Dodge & Swartz 1965), making a relationship to drug the fart appear less likely. In addition this parient was receiving penicillin. It is of interest to note that conscribing was detected in the CSF, and that the CSF plasma contriduct ratio was 0.43. ω compared to 0.11 in Case 1. This may not be surprising in view of the offect of meninguis on the permeability observationies of the blood-broin barrier.

Increased permeability of the blood brain barrier has also been reported in conal failus (Fishman & Raskin 1965, Smithers et al. 1975). This could explain why in Case 2 the comparatively high considing level on the sixteenth day was not associated with twitching, as by this time the patient was not urasmic, and therefore less concluding would have crossed by blood-brain barrier.

Previous reports have linked constitute nearetoxicity and retail failure (McMillen et al. 1978; Wood et al. 1978). Grave et al. (1973) noted twisching in a min of 81 given cineridal 200 regain bourly i.v. for crossee gastritis following prostatectomy. At the time he was in real failure with a blood area of 21 minold. It is of interest that no cases of neurotoxicity well reported in a large series of patients given cimetaline following renal transplantation (1978):

There are no previous reports in the literature of cimeridine crossing the blood-brain batter in man. Extensive toxicological and pharmagological studies in animals have failed to detect cimerature in the central network system and neutroloxicity has not been betted (Brimblecomis & Duncan 1977, Loslie & Walker 1977, Cross 1977). The fact that hyperprolactionemia con brindwest by cimeridine (Delle Fave et al., 1977), suggests that the drug may cross the blood-brain barrier in certain circumstances. The precise mechanism for this effect remains unclear (Burland et al., 1979).

The cases presented in this report suggest that cimetidine may be neurotoxic in debilitated patients especially when the blood-brain burner is compromised. Until there have been further studies correlating clinical signs with levels of cimetidine in blood and CSF, cimetiding should

be used with causion concliding daily down

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Jimetidine 360 mg twicz dogy venty four hours later (after a free a neventional anticodyalsants (after and magnesiam were at trapen was 1.75 mg t. CSp amoud and after 1.4 hours go neconsistes the subsequently trapes was refused.

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ssing the blood-brain barot animals have failed to detest t been noted (Bramblecombo hyperprofactionemia can be ag may cross the blood-brain this effect remains unifer

be neurotoxic in debilitated Until there have been further tand CSF, cimetidine should be used with castion in read impairment. Where read impairment is significant the total application dutly desage thrould not exceed 400 mg, as is suggested in the official data sheet.

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Three Cases of anochholopath) isociated with cimetidine therapy are presented. All three gateris had imported tend function and had received cimetidine to standard design at the another amounts of concliding were present in the CSF of two patients, confirming that the grad can cross the blood brain burrier in man under certain crossmetances. Where renal impaintment is significant, the food daily design of the drug should be appropriately reduced.

please Commence We think Professor A.F. Lant, Dr.R. D. Starrock and Dr.L. W. Longbridge for permission to report these cases; Dr.R. M. Lee, who performed the concentions estimations as pleased and CSF; Dr.A.C. Flind and Dr.B. Dickson of Smith Kline and French Laboratories for their helpful comments; and Mr. D. Jockson of May and Baker Lid for the inciroindayole estimations.

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